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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/521,634	10/11/2005	Brian Seed	00786/432002	4930
21559	7590	03/26/2008	EXAMINER	
CLARK & ELBING LLP 101 FEDERAL STREET BOSTON, MA 02110				WILSON, MICHAEL C
ART UNIT		PAPER NUMBER		
		1632		
			NOTIFICATION DATE	
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			03/26/2008	
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentadministrator@clarkelbing.com

<b>Office Action Summary</b>	<b>Application No.</b>	<b>Applicant(s)</b>	
	10/521,634	SEED ET AL.	
	<b>Examiner</b>	<b>Art Unit</b>	
	Michael C. Wilson	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) Responsive to communication(s) filed on 20 December 2007.
- 2a) This action is **FINAL**.                  2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) Claim(s) 1-12, 18 and 19 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) Claim(s) \_\_\_\_\_ is/are allowed.
- 6) Claim(s) 1-12 18 19 is/are rejected.
- 7) Claim(s) \_\_\_\_\_ is/are objected to.
- 8) Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on \_\_\_\_\_ is/are: a) accepted or b) objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) All    b) Some \* c) None of:  
 1. Certified copies of the priority documents have been received.  
 2. Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.  
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

- |  |   |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)   | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                         | Paper No(s)/Mail Date. _____ .                                    |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)<br>Paper No(s)/Mail Date _____ . | 5) <input type="checkbox"/> Notice of Informal Patent Application |
|  | 6) <input type="checkbox"/> Other: _____ .                        |

## **DETAILED ACTION**

Claims 13-17 and 20-39 have been canceled. Claims 1-12, 18 and 19 remain pending and are under consideration.

Applicant's arguments filed 12-20-07 have been fully considered but they are not persuasive.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

### ***Claim Rejections - 35 USC § 112***

Claims 1-12, 18 and 19 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The rejection of claim 1 regarding the metes and bounds of what applicants consider "substantial sequence identity" has been withdrawn in view of the amendment.

The rejection of regarding the use of "cell(s)" in claim 1 has been withdrawn in view of the amendment.

Claim 2 as amended is indefinite because the structure of the artificial chromosome is not clearly set forth. It cannot comprise one nucleic acid sequence that is at least 90% identical to two regions of homology. It must comprise one nucleic acid sequence that is each at least 90% identical to the first region of homology and a second nucleic acid sequence that is each at least 90% identical to the second region of homology. The step in claim 2 is also confusing because it occurs prior to those in claim 1 but does not clearly set forth the structure of the cassette (i.e. having a first

region, second region, selectable marker, etc). Nor does it clearly set forth introducing the cassette into host cells (yeast) comprising the artificial chromosome. Clarification is required.

Claim 4 as amended remains indefinite because it does not clearly further limit claim 2. The limitation as amended fails to clearly set forth inserting a circular vector comprising the linear DNA into the host cells (yeast) and cleaving the vector to generate the linear DNA. In addition, further limiting the linear DNA as written is a misnomer because the limitation is actually a method step. The limitation in claim 4 should be written as a method step.

Claim 9 remains indefinite because “the activity of the protein encoded by a nucleic acid of interest that includes said first or second region of said endogenous chromosome” lacks antecedent basis.

Claim 10 as amended is indefinite because “the amount of functional protein...” lacks antecedent basis.

The rejections of claims 11 and 12 have been withdrawn in view of the amendment.

#### ***Claim Rejections - 35 USC § 102***

The rejection of claims 1-12, 18 and 19 under 35 U.S.C. 102(a) as being anticipated by Wilson (Analytical Biochem., Sept. 15, 2001, Vol. 296, No. 2, pg 270-278) has been withdrawn because the YAC system described by Wilson was used to isolating homologously recombined gene cassettes which were then cloned into plasmid.

Wilson cultured yeast with linear DNA comprising a cassette encoding a selectable marker operably linked to a promoter (pg 270-271, Cassettes A-G). The cassettes were PCR'd to have overlapping ends homologous to the IL-10R $\alpha$  or PPAR $\gamma$  genes (pg 271, col. 2, PCR of the targeting gene). Primer pairs used to make the cassette had a first and second region of homology having at least 90% sequence identity to the IL-10R $\alpha$  or PPAR $\gamma$  genes (pg 272, Table 1). The cassettes made by Wilson are equivalent to the cassette in section (a) of claim 1.

Amplified cassettes were transformed into YAC-containing yeast strains comprising a nucleic acid sequence that was at least 90% identical to said first and second regions of homology such that recombination occurs (pg 271, col. 2, Transformation of yeast strains), which is equivalent to the step in claims 2 and 4.

The homologously recombined locus (made in YAC-containing yeast) was isolated as a 6-15 kb piece of DNA and then cloned into plasmid (pg 272, Isolation of the targeted locus; see also the "Overview of the procedure" on pg 273-275, specifically pg 275, col. 1, line 1). ES cells were transfected with linearized targeting vector. Transfecting ES with a plasmid comprising 6-15 kb fragments isolated from YAC is equivalent to inserting an "artificial chromosome" as into mammalian cells as claimed. "Artificial chromosome" encompasses any chromosome or fragment thereof having an artificial modification (pg 14, line 17), which is equivalent to the fragments from the yeast artificial chromosome isolated by Wilson, put into plasmid and inserted into ES cells.

Transformation (claim 3) is the same as transfection taught by Wilson.

In the PPAR $\gamma$  example, contiguous regions of exon 5 are deleted (paragraph bridging pg 276-277; pg 277, Fig. 4), which is equivalent to claims 5 and 6.

In the IL-10R $\alpha$  example, two exons and an intervening intron are deleted (pg 275, col. 2, Examples, line 9), which is equivalent to 7 and 8.

Southern blot analysis showed the genes were deleted, which inherently indicates the amount of functional protein was less than 25% as claimed as in claim 10.

Fig. 2 shows the various selectable marker strategies, which are equivalent to claim 11 and 12.

The ES cell clones were used to make germline-transmitting chimeras (pg 277, last sentence in the caption of Fig. 4), which is equivalent to claim 19 because the germline-transmitting chimeras inherently transmit the deletion to both somatic and germ cells.

Applicants argue Wilson transfected ES cells with plasmid not artificial chromosomes as claimed. Applicants argue claim 1 requires inserting an artificial chromosome directly into mammalian cells. Applicants' arguments are not persuasive. Claim 1 does not require "transfected" mammalian cells with artificial chromosomes or inserting the artificial chromosome "directly" into the cells. Claim 1 merely requires inserting artificial chromosomes into mammalian cells. Furthermore, the definition on pg 14, "artificial chromosomes" encompasses artificial chromosome fragments. Therefore, the 6-15 kb homologously recombined cassette fragments isolated from YAC described by Wilson (sentence bridging pg 274-275) are "artificial chromosomes" as claimed. The "artificial chromosomes" described by Wilson are "inserted" into mammalian cells as

claimed because they are put into ES cells using a plasmid. Claim 1 is not limited to inserting an “artificial chromosome” in the absence of a plasmid. Accordingly, the teachings of Wilson meet the limitation of “inserting” an “artificial chromosome” into a mammalian cell as claimed.

***Conclusion***

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson who can normally be reached at the office on Monday, Tuesday, Thursday and Friday from 9:30 am to 6:00 pm at 571-272-0738.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Art Unit: 1632

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

If attempts to reach the examiner are unsuccessful, the examiner's supervisor, Peter Paras, can be reached on 571-272-4517.

The official fax number for this Group is (571) 273-8300.

Michael C. Wilson

/Michael C. Wilson/  
Patent Examiner